

AF/1635



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PATENT

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In re: Glucksmann, et al.

Appl. No.: 09/464,685

Group Art Unit: 1635

Filed: 12/16/99

Examiner: A. Wang

For: 2/1 RECEPTOR, A NOVEL G-PROTEIN COUPLED RECEPTOR

October 29, 2001

REPLY
Brief

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REPLY BRIEF

Sir:

This Reply Brief is filed in response to the Examiner's Answer, mailed 8/28/01.

Status of Amendments

An Amendment After Final Action was filed October 29, 2001 to cancel subject matter from claims 73 and 81. Applicants note that U.S. Patent No. 6,063,596 has issued from the PCT application cited by Applicants during prosecution (Int'l. Pub. No. WO 99/29849; see paper 8 including IDS initialed by Examiner in Office Action mailed 8/25/00). Because the claims of this issued patent read on the proposed claims of the present application, Applicants filed the amendment in order to reduce issues on appeal. A copy of the claims prior to this amendment can be found attached to the Appeal Brief filed in this case on July 10, 2001; the claims attached hereto are shown as if the changes suggested in the Amendment After Final Action had been entered.

Introduction

The Examiner has raised several new arguments in the Examiner's Answer and has renewed grounds for the rejection that were previously overcome by the Appellants. In the final Office Action, the Examiner states, "Applicants have not clearly demonstrated that the cloned nucleic acid and its encoded polypeptide is actually a GPCR as was noted in the utility rejection,"

but "Applicants do indeed provide multiple well established and specific utilities for a GPCR." See, Office Action dated February 12, 2001, page 3. In the Examiner's Answer, the Examiner agreed with Appellants' statement of the issues in the Appeal Brief that the single issue was whether 2871 is a GPCR (Examiner's Answer, page 2). However, the Examiner proceeds to set forth a new ground for the utility rejection, indicating that even if Applicants establish 2871 as a GPCR, members of the GPCR family of polypeptides do not have well-established utility. See, Examiner's Answer, pages 4-5.

The Examiner also cites a new reference in the Examiner's Answer in support of the argument that a protein's sequence may not be used to predict its function (Attwood (2000) *Science* 290:417-473). The Examiner's Answer further includes citations to two references that were cited in the first Office Action as a grounds for rejection under 35 U.S.C. § 101, but that were not cited in the final Office Action. The fact that these references were not cited in the final Office Action led Appellants to believe that the rejection had been overcome to the extent that it was based on these references, and therefore the Examiner's arguments were not addressed in detail in the Appeal Brief.

Appellants note that this change in direction by the Examiner, which was not explained, is a practice which makes patent prosecution more difficult. This practice serves to obscure the basis for the rejection and runs the risk of unfairly prejudicing applicants' nascent property rights in their patentable subject matter. As stated by the Federal Circuit in *In re Oetiker*, "[t]he examiner cannot sit mum, leaving the applicant to shoot arrows in the dark hoping to somehow hit a secret objection harbored by the examiner." 977 F.2d 1443, 24 USPQ2d 1443, 1447 (Fed. Cir. 1992) (Plager, J., concurring).

Because the Examiner previously admitted that GPCRs have "multiple well-established and specific utilities," Appellants did not fully address the utility of GPCRs in the Appeal Brief. It is requested that the rejection be withdrawn or prosecution be reopened to give Appellants a fair opportunity to respond to the new and renewed grounds of rejection. However, should the rejection not be withdrawn and prosecution not be reopened, Applicants here present these arguments in response to the Examiner's new and revived grounds of rejection. Responses to the Examiner's new and revived arguments are addressed below in section A, while the issue of

utility of the present invention is discussed below in section B.

Argument

2871 Encodes a G-Protein Coupled Receptor

A. The evidence presented by the Examiner does not address the methods used by the Appellants to determine 2871 receptor function.

1. Berendsen is directed to the de novo prediction of protein tertiary structure from primary structure, not the prediction of protein function based on the presence of conserved functional domains.

In the first Office Action and the Examiner's Answer, the Examiner cited Berendsen *et al.* (1998) *Science* 282:642-643 in support of the argument that protein activity predictions based on functional domains are unpredictable. Because this reference was not cited in the final Office Action, Appellants believed that the rejection had been overcome to the extent that it was based on this reference. However, the Examiner has cited Berendsen in the Examiner's Answer and thus it will be addressed here.

The teachings of Berendsen are directed to methods of predicting a protein's tertiary structure from its primary sequence. Berendsen states, "[t]he prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics," and then proceeds to discuss computer simulations of protein folding. See Berendsen at 642. In the Examiner's Answer, the Examiner appears to acknowledge that Berendsen is not directed to the functional domain based predictions of protein function utilized by Appellants, but notes that "the activity of any protein or polypeptide is dependent on its structure." (Examiner's Answer, page 9) While Appellants agree that some regions of a protein must retain a certain conformation in order for the protein to be active, it does not follow that a protein's tertiary structure must be known in order to determine the activity of that protein. In fact, three-dimensional structures have been elucidated for only a very few of the thousands of proteins having known biochemical or physiological activity. Accordingly, the caveats regarding predictions of tertiary structure found in Berendsen are not relevant to methods for predicting

protein function used by the Appellants.

2. *Galperin is directed to context-based methods of predicting protein function, not to predictions of protein function based on the presence of functional domains.*

In the first office action, the Examiner cited Galperin *et al.* (2000), *Nature Biotechnology* 18:609-613, in support of the argument that a protein's function cannot be predicted from the presence of conserved functional domains. This reference was not cited in the final Office Action, leading Appellants to believe that the rejection was overcome to the extent that it was based on this reference. However, the Examiner has cited the reference in the Examiner's Answer and thus it will be addressed here.

The teachings of Galperin are directed to the prediction of protein function using comparative genomic approaches. The abstract for the Galperin reference states, "[s]everal recently developed computational approaches in comparative genomics go beyond sequence comparison. By analyzing phylogenetic profiles of protein families, domain fusions, gene adjacency in genomes, and expression patterns, these methods predict many functional interactions between proteins and help deduce specific functions for numerous proteins." The authors then proceed to discuss the strengths and weaknesses of these genomic context-based methods of functional prediction. Accordingly, the primary teachings of Galperin are not directed to the methods used by the Appellants to predict 2871 function.

In rebutting Appellants' arguments, the Examiner quotes Galperin: "sequence comparison methods, even the best ones, are of little help when a protein has no homologs in current databases or when all hits are to uncharacterized gene products." While Appellants agree that sequence similarity with uncharacterized gene products cannot be used to determine a protein's activity, this caveat does not apply to determine the function of the 2871 receptor. In the present case, the function of the 2871 receptor was determined based on the presence of sequence similarity with a conserved functional domain characteristic of the rhodopsin family of GPCR's. As described fully in Appellants' Appeal Brief and illustrated in Appendix E of the same, this conserved functional domain was elucidated from the sequences of a number of

rhodopsin-family GPCR's having known biochemical activities. Accordingly, Galperin's statement that "sequence comparison methods...are of little help...when all hits are to uncharacterized gene products" is true but does not undermine the reliability of the methods of functional prediction used by the appellants.

The only additional teachings that Galperin provides regarding prediction of protein function based on sequence similarity with proteins of known function are also supportive of the strength and reliability of the methods used in the present application. Galperin states (page 613, column 1) that comparative genomic methods of predicting protein function discussed in the reference "provide a useful extension of, and in a sense a genome-based framework for, sequence and structural methods which remain the cornerstone of computational genomics." Thus, Galperin distinguishes between the comparative genomics-based methods of functional prediction reviewed in the reference and the pattern based methods for functional prediction used by the Appellants, and further demonstrates that the authors consider the approach used by Appellants to be reliable.

3. *Attwood distinguishes between the reliability of module-based prediction of protein function and pattern-based prediction of protein function and presents arguments supporting the diagnostic reliability of pattern databases.*

The Examiner's Answer includes a citation to a new reference (Attwood (2000) *Science* 290:471-473) in support of the argument that sequence similarity cannot be used to predict protein function. Specifically, the Examiner cites the statement: "[i]f the best hit in a database search is a match to a single domain module, it is unlikely that the function annotation can be propagated from the parent protein to the query sequence," and "[t]he presence of a module tells little of the function of the complete system; knowing most of the components of a mosaic does not allow us easily to predict a missing one, and modules in different proteins do not always perform the same function." Attwood (2000) *Science* 290 at page 472, column 2. A careful reading of the Attwood reference makes it clear that these statements refer not to the prediction of protein function based on the presence of a conserved functional domain, but rather to the prediction of function based on the presence of a single motif or module. Such modules are

defined by Attwood as "autonomous folding units that often function as protein building blocks, forming multiple combinations of the same module or mosaics of different modules." *Id.* In the present case, Appellants have determined the function of the 2871 receptor based on the fact that 255 contiguous amino acids of the 2871 polypeptide provide an excellent fit to the empirically-derived model of the GPCR family that includes rhodopsin. This statistical model is not solely based on the presence of a single autonomous folding unit.

The differences between the reliability of motif or module-based methods of protein function prediction and functional domain-based methods of function prediction are discussed in greater detail in Attwood (2000) *Int. J. Biochem. Cell Biol.* 32:139-155 ("*IJBCB*," provided as Appendix G), a more comprehensive review article published by Attwood in the same year as the reference cited by the examiner. In this reference, Attwood teaches that while functional prediction methods based on the presence of a single motif may be problematic because matches to single motifs lack biological context (see Attwood, *IJBCB* at 144), many of the flaws inherent in these single motif-based methods are overcome in pattern databases such as Pfam. Attwood states:

"[p]attern databases offer several benefits: (i) by distilling multiple sequence information into family descriptors, trivial errors in the underlying sequences may be diluted; (ii) annotation errors may be quickly spotted if the description of one sequence differs from that of its family; and (iii) they allow specific diagnoses, placing individual sequences in a family context for a more informed assessment of possible function."

Attwood, *IJBCB* at 153.

Attwood also teaches the diagnostic advantages of manually-generated databases such as Pfam (which is based on hand-edited seed alignments; see Attwood, *IJBCB* at 149). Attwood states, "manually annotated databases are set apart from their automatically created counterparts by virtue of (i) providing *validation* of results and (ii) offering detailed information that helps to place conserved sequence information in structural or functional contexts." (Attwood, *IJBCB* at 152). Attwood further states that while pattern databases are small in comparison with sequence repositories, "their diagnostic potency ensures that pattern databases will pay an increasingly

important role as the post-genome quest to assign functional information to raw sequence data gains pace." (Attwood, *IJBCB* at pp. 153-154) Thus the teachings by Attwood regarding pattern databases, particularly manually-generated pattern databases, are strongly supportive of the reliability of these techniques.

Thus, the Examiner seizes on a single brief review article by Attwood about caveats of sequence comparison methods to discredit sequence comparison methods in general (Examiner's Answer, page 7, "protein function cannot be ascertained from analysis of its components.") Applicants agree generally with Attwood's argument in the new reference cited by the Examiner that predictions of protein function based on a single motif are not necessarily reliable. However, those of skill in the art distinguish between the presence of a single motif in a protein and the presence of configurations of multiple motifs, or a pattern, which is diagnostic of a particular protein family.

Attwood has published a number of articles describing patterns that are diagnostic of G-protein coupled receptors¹, and is known as one of the creators of the PRINTS sequence comparison method and database. Perhaps most pertinent here is an article published by Attwood after the article cited by the Examiner, entitled: "A compendium of specific motifs for diagnosing GPCR subtypes." Attwood (2001) *TRENDS in Pharmacological Sciences* 22(4): 162-165 ("TiPS," provided as Appendix H). In this article, Attwood discusses the differences between several sequence comparison methods and describes the use of her PRINTS methods and database for the analysis of GPCRs (available at <http://bioinf.man.ac.uk/cgi-bin/dbbrowser/fingerPRINTScan/muppet/FPScan.cgi>, as indicated in Figure 1). See Attwood, *TiPS* at 164.

A PRINTS analysis of the closest publicly disclosed polypeptide sequence to the subject of the present application (*i.e.*, the sequence disclosed in U.S. Patent No. 6,063,596 as SEQ ID NO: 3) shows an identification of the "GPCRRHODOPSN" fingerprint, with an E-value of $3.1e^{-}$

¹ Attwood's work includes: Attwood and Beck (1994), *Protein Eng.* 7(7): 841-848, entitled "PRINTS—a protein motif fingerprint database"; Attwood and Findlay (1994) *Protein Eng.* 7(2): 195-203, entitled "Fingerprinting G-protein Coupled Receptors"; Attwood *et al.* (1991) *Gene* 98(2): 153-159, entitled "Multiple Sequence Alignment of Protein Families Showing Low Sequence Homology: A Methodological Approach Using Database Pattern-matching Discriminators for G-protein-linked Receptors."

²⁹ and a P-value of $1.2e^{-34}$ (see output, attached as Appendix I). As indicated in the documentation for PRINTS also available at this site, “[t]he reported P-value of any fingerprint result is the product of the p-values for each motif. The motif p-values represent the probability that a comparison between the motif and a random sequence would achieve a score greater than or equal to the score attributed to the match between your query sequence and the motif.” The E-value is the expected number of occurrences of sequences scoring greater than or equal to the query’s score. Thus, the very low P-value and E-value obtained from Attwood’s PRINTS analysis concurs with the Pfam diagnosis described by Applicants that the 2871 sequence is a GPCR. Accordingly, the Examiner’s use of Attwood to discredit sequence comparison methods in general is inconsistent with Attwood’s work, which strongly supports the conclusion that the 2871 sequence is a GPCR.

4. *The Examiner’s failure to credit the predictive power of sequence comparison methods is at odds with accepted practice in the art.*

The Examiner notes (Examiner’s Answer, paper number 18 mailed 8/28/01, page 3) that “[m]oreover, the specification discloses that the cloned GPCR shares a high score with the seven transmembrane rhodopsin family,” and further states on page 4 that “the specification notes that proteins with putative seven transmembrane domains, much like applicants, are not necessarily GPCRs such as *boss* and *fz* cloned from *Drosophila*.” The Examiner also states (Examiner’s Answer, page 6-7) that “Figure 2 provides for only the DRY triplet and low sequence homology.” Based partly on this line of reasoning, the Examiner asserts that the specification lacks “a specific and substantial utility [and] a well established utility.”

This line of reasoning by the Examiner is inconsistent with the understanding of one of skill in the art of Pfam alignments, and of sequence comparisons in general. As known to those of skill in the art (and described in the Pfam documentation available at <http://pfam.wustl.edu/faq.shtml>), Pfam alignments do not display homology between pairs of sequences but rather display the fit of a particular query sequence to a particular protein family model. As discussed on the Pfam “Help Page:FAQ” available at the address above, complaints [like the Examiner’s present complaint] about the quality of the alignments generally arise

“because people aren’t used to looking at multiple alignments of hundreds or thousands of sequences. Remember that a rare insertion in even just one sequence [in the protein family] means having to open a gap in the whole alignment: Pfam full alignments look very gappy for this reason, but in fact they’re not.”

The Examiner also ignores that *boss* (bride of sevenless) and *fz* (frizzled) show low similarities to GPCR domains in Pfam alignments. One of skill in the art understands that Pfam alignments of *boss* and *frizzled* with the highest-scoring seven transmembrane domain models for each (7tm_3 and 7tm_2, respectively) have negative scores. In contrast, the 2871 sequence has a high positive score for the rhodopsin subfamily that is described by Pfam model 7tm_1. Pfam “bit scores” represent the log base 2 of a ratio. In the numerator of this ratio is the probability of the sequence given the hypothesis that the sequence belongs to the protein family being modeled. In the denominator of this ratio is the probability of the sequence given the hypothesis that the sequence was generated according to a random background model. Thus, the bit score of 183 for protein 2871 with the Pfam 7tm_1 model means this protein sequence is 2^{183} times more likely to be observed if it were generated by the 7tm_1 model than if the sequence were generated by the other model. We note that 2^{183} (about 1.2×10^{55}) greatly exceeds the estimated number of atoms comprised by the planet Earth. In contrast, the optimal score for *boss* to a GPCR family is -53, and the optimal score for *frizzled* is even lower, at -112. In other words, the sequence of *boss* is 2^{53} times more likely to be observed if it were generated by the random background model than if it were generated by the best-fitting GPCR model. Although 2^{53} does not exceed the estimated number of atoms that are comprised by the planet Earth, we note that 2^{53} is an extremely large number (about 9×10^{15}). Thus, contrary to the Examiner’s arguments, the fact that the *boss* and *frizzled* proteins have seven transmembrane domains does not detract from Applicants’ evidence that the sequences of the present invention are GPCRs.

The Examiner has attacked Applicants’ use of sequence comparison methods by quoting caveats largely out of context. As one of skill in the art is aware, any methodology is fallible to some degree and there are always exceptions to a rule; thus, most if not all articles describing sequence comparison methods also discuss the shortcomings of those methods. The Examiner seizes on these caveats to discredit the use of sequence comparison methods. The Examiner’s

approach is at odds with that of the art, which has embraced sequence comparison methods, particularly as those methods have advanced in sophistication with the rapid advances of the genomic era.

A brief survey of PubMed (accessible at <http://www.ncbi.nlm.nih.gov/>) shows dozens of peer-reviewed, scientific articles published every month describing novel discoveries of sequences having strong identity to sequences of known function. The acceptance of sequence comparison methods by the art is evidenced in many places. For example, Mount (2001) *Bioinformatics: Sequence and Genome Analysis* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), page 282 (provided as Appendix J) states that “[d]atabase similarity searches have become a mainstay of bioinformatics.” Mount goes on to explain that, “[a]s a rough rule, if more than one-half of the amino acid sequence of query and database proteins is identical in the sequence alignments, the prediction is very strong. As the degree of similarity decreases, confidence in the prediction also decreases. The programs used for these database searches provide statistical evaluations that serve as a guide for evaluation of the alignment scores.” As noted by Gusfield (1997) *Algorithms on Strings, Trees, and Sequences: Computer Science and Computational Biology* (Cambridge University Press, New York, New York), at pages 212-213 (provided as Appendix K),

[s]equence comparison, particularly when combined with the systematic collection, curation, and search of databases containing biomolecular sequences, has become essential in modern molecular biology. * * * The first fact of biological sequence analysis: In biomolecular sequences (DNA, RNA, or amino acid sequences), high sequence similarity usually implies significant functional or structural similarity. Evolution reuses, builds on, duplicates, and modifies “successful” structures (proteins, exons, DNA regulatory sequences, morphological features, enzymatic pathways, *etc.*).

* * *

‘Today, the most powerful method for inferring the biological function of a gene (or the protein that it encodes) is by sequence similarity searching on protein and DNA sequence databases. With the development of rapid methods for sequence comparison, both with heuristic algorithms and powerful parallel computers, discoveries based solely on sequence homology have become routine.’ [citation omitted] * * * It is now standard practice, whenever a new gene is

cloned and sequenced, to translate its DNA sequence into an amino acid sequence and then search for similarities between it and members of the protein databases.”

Another indicator of the importance of sequence comparison methods to the “new paradigm” of modern molecular biology is the fact that the most-cited paper of 1990-1998 is the publication describing BLAST: Altschul (1990) *J. Mol. Biol.* 215: 403, entitled “Basic Local Alignment Search Tool.” (citation figures available at <http://www.isinet.com/isi/hot/research>) (provided as Appendix L). Accordingly, the Examiner’s efforts to discredit sequence comparison methods in general is inconsistent with the art, which supports the use of sequence comparison methods and thus the conclusion that 2871 is a GPCR.

5. Despite the fact that the histamine receptor family is divergent, members of these families were identified as GPCRs based on sequence similarity with known GPCRs.

In the Appeal Brief, Appellants cited Nguyen *et al.* (2001) *Mol. Pharmacol.* 59:427-433 which describes the identification of the histamine receptor H₄ based on sequence similarity with known GPCRs. In response, the Examiner has cited the teaching by Nguyen that the histamine receptors H₁, H₂, and H₃ share less than 35% identity with one another and each has greater identity with other aminergic receptors. This statement by Nguyen supports rather than discredits the reliability of the methods of functional prediction used by the Appellants, as it demonstrates that the activity (in this case the G-protein mediated signal transduction activity) of a protein can be predicted based on sequence identity of less than 35%.

Despite the fact that histamine receptors share only moderate sequence identity with each other, the H₁, H₂, H₃, and H₄ receptors were each recognized as being a G-protein coupled receptor having G-protein mediated signal transduction activity based on sequence identity. For example, Yamashita *et al.* (1991) *Biochem.* 88:11515-11519 (provided as Appendix M) describe the cloning of the H₁ receptor and note that “[t]he histamine H₁ receptor is highly similar to other G protein-coupled receptors.” Yamashita at 11518. Similarly, Gantz *et al.* (1991) *Proc. Natl. Acad. Sci.* 88:429-433 (provided as Appendix N) describe the cloning of the H₂ receptor and

note that "comparison of the deduced amino acid sequence to that of other G-protein-linked receptors with presumed seven-transmembrane motifs revealed extensive homology." The H₃ histamine receptor was identified and cloned based on a high degree of sequence similarity with biogenic amine GPCRs (Lovenberg *et al.* (1999) *Mol. Pharmacol.* 55:1101-1107, provided as Appendix O). Finally, as described in the Appeal Brief, Nguyen *et al.* describe the cloning of the H₄ receptor based on a query of GenBank to identify sequences sharing sequence similarity with GPCRs. Thus, the G-protein mediated signal transduction activity of all of the histamine receptors was accurately predicted based on sequence similarity with known GPCRs. Accordingly, the Examiner's attempt to use Nguyen to discredit functional prediction methods is misguided.

6. *The tumor suppressor activity of p73 was predicted based on sequence identity with the known tumor suppressor p53.*

In the Appeal Brief, Appellants cite Dickman *et al.* (1997) *Science* 277:1605-1606, which teaches that the tumor suppressor activity of the p73 polypeptide was determined based on sequence similarity with the transcription activation, DNA-binding, and oligomerization domains of the known tumor suppressor protein p53. In response, the Examiner argues that Dickman teaches that the p73 gene is deleted in certain cancers. However, a careful reading of Dickman finds that the original determination of p73 protein's tumor suppression activity was made on the basis of sequence similarity alone. Dickman teaches that p73 was identified in a screen for genes that respond to certain immune system regulators. Dickman states, "[w]hen the French team sequenced the many potential targets their screen had turned up, they were shocked to find out that one false positive had remarkable similarities to p53." Dickman at 1605. It was only after p73's tumor suppression activity had been predicted on the basis of sequence similarity with p53 that the investigators thought to look for alterations in the p73 gene in cancer patients. Thus, Dickman is an excellent example of the value of sequence comparison-based approaches to discovery of new genes.

7. *Kliewer demonstrates the successful identification of novel nuclear receptors based on sequence similarity with the ligand-binding domain of known nuclear receptors.*

In the Appeal Brief, Appellants cite Kliewer *et al.* (1998) *Cell* 92(1): 73-82 as an additional example of the accurate determination of a protein's function based on the presence of functional domains. The Examiner seeks to discredit this argument by noting that the PXR.1 amino acid sequence is identical to the PXR.2 amino acid sequence except for a 41 amino acid deletion resulting from alternative splicing. This statement misses the point of the reference, which does not teach the isolation of the PXR.2 coding sequence based on the PXR.1 coding sequence but instead describes the cloning of both the PXR.1 and PXR.2 coding sequences based on sequence identity with motifs characteristic of known nuclear receptors. Kliewer states, "[i]n an effort to identify new member of the nuclear receptor family, we performed a series of motif searches of public EST databases. These searches revealed a clone . . . that had homology to the ligand-binding domain of a number of nuclear receptors." Kliewer at 74. Kliewer teaches that this EST was then used to clone the nuclear receptor PXR.1 and its splice variant PXR.2. Thus, Kliewer describes yet another successful use of sequence similarity with functional domains to predict protein function.

B. *The evidence presented by Applicants supports a finding that the present invention satisfies the requirement of utility.*

Applicants again note that these arguments are presented for the first time on appeal because the Examiner earlier indicated that the only issue was whether the disclosed sequence actually was a GPCR. Now, the Examiner asserts that even if the disclosed sequences are GPCRs, utility is not established. Because the Examiner has changed the utility rejection, Applicants have not had the opportunity to fully address the Examiner's arguments. Applicants here present these arguments in response to the Examiner's new and revived grounds of rejection.

1. *The 2871 receptor is useful in selectivity screening and therefore has a "well-established" utility.*

The Examiner has rejected claims 73, 74, 81, and 88-96 under 35 U.S.C. §101 on the grounds that the claimed invention "lacks patentable utility." (Feb. 12, 2001 Office action page 3). This does not correctly reflect the view in the art, where it is known that "[h]istorically, the superfamily of GPCRs has proven to be among the most successful drug targets and consequently these newly isolated orphan receptors have great potential for pioneer drug discovery." Stadel *et al.* (1997) *Trends Pharmacol. Sci.* 18:430-436; provided as Appendix P). Those of skill in the art recognize that the identification of a novel member of the G-protein coupled receptor family provides an immediate benefit. In addition to serving as reagents and targets in the diagnosis and treatment of 2871-mediated disorders as described in the specification on page 48 *et seq.*, all members of the GPCR protein family have utility in selectivity screening of candidate drugs that target GPCRs. It is known in the art that the clinical usefulness of a therapeutic compound is determined not only by its ability to bind and modulate a molecular target of interest, but also by its selectivity. Drugs that bind selectively to their molecular target are highly preferred over those that bind to structurally-related molecules, as the selective compounds are far less likely to have unwanted side effects in clinical use. See, for example, Hartig (1993) *NIDA Res. Monogr.* 134: 58-65, entitled, "The use of cloned human receptors for drug design," provided as Appendix Q; Fraser (1995) *J. Nucl. Med.* 36 (6 Suppl): 17S-21S, provided as Appendix R. Thus, an important component of any drug development strategy is determining the selectivity of the candidate drug for the molecular target of interest over structurally-related polypeptides. The effectiveness of selectivity screening in uncovering interactions that may result in undesirable clinical side-effects increases in proportion with the number of structurally-related polypeptides screened. In this situation, the usefulness of these structurally-related polypeptides is not dependent on their biological role or ligand-binding properties; their utility comes from the fact that they share significant sequence identity with the molecular target of the candidate drug.

An example of the use of orphan receptors in selectivity screening is found in Goodwin *et*

al. (2000) *Molecular Cell* 6:517-526, provided as Appendix S. This reference is directed to the identification of a specific agonist for FXR, an orphan nuclear receptor that regulates bile acid synthesis and is a target in the treatment of cholestasis. (See generally, Niesor *et al.* (2001) *Curr. Pharm. Des.* 7: 231-259). Goodwin states that many previously-identified FXR ligands interact with other proteins including bile-acid-binding proteins and transporters (Goodwin at page 518, column 1). In order to identify a compound that selectively modulates FXR, the authors screened for compounds that modulated FXR activity and then tested these compounds for their ability to activate other nuclear receptors that share structural similarity with FXR. Figure 1C of Goodwin shows that the compound GW4064 potently activates FXR but does not modulate the activity of the other nuclear receptors tested. Note that the nuclear receptor panel screened in Figure 1C includes the orphan nuclear receptors SHP-1 and LRH-1 in addition to receptors having previously-identified ligands, illustrating that studies often include orphan receptors.

More than 50% of prescription drugs act at GPCR targets, further showing the importance of GPCRs in screens for effective drugs. However, some of these drugs have efficacy problems and limiting side-effects because the compounds do not differentiate between receptor subtypes. See generally, Stadel *et al.*, (1997) *Trends Pharmacol. Sci.* 18: 430 (Appendix P); Lee and Kerlavage (1993) *Molecular Biology of G-Protein-Coupled Receptors*, 6 DN&P 488 (provided as Appendix T). Accordingly, because the GPCR protein family includes a number of key drug targets, members of this family share a common use in the selectivity screening of candidate drugs. The 2871 receptor shares a high degree of identity with the rhodopsin family of GPCRs (see specification Figure 2). This rhodopsin GPCR family includes targets for the treatment of numerous disorders including depression, anxiety, migraine, asthma, hypertension, and cardiovascular disorders. Thus, all members of this important class of GPCRs, including those disclosed in the present invention, have a specific, immediately available, real world utility in the selectivity screening of drugs directed at GPCR targets.

The 2871 receptor shares a high degree of identity with the rhodopsin family of GPCRs and is expressed in tissues including those of particular clinical significance to hematological disorders, such as hematopoietic cells (see Figure 7; see also Figures 5-6 and specification pages 6 and 19). Indeed, the 2871 gene is expressed at significant levels in all blood cell progenitors

analyzed by the inventors. It is highly expressed in bone marrow (CD34⁺), G-CSF-mobilized peripheral blood (containing circulating progenitors derived from bone marrow) and is moderately expressed in CD34⁺ adult bone marrow and CD34⁺ cord blood cells. It is also highly expressed in megakaryocytes as well as CD41⁺ (CD14⁺) bone marrow cells. G-CSF-mobilized peripheral blood contains circulating progenitors derived from bone marrow. Accordingly, expression of the 2871 gene is relevant for treating disorders associated with the formation of differentiated and/or mature blood cells, such as anemia, neutropenia, and thrombocytopenia.

The therapeutic and economic benefits that can result from selectivity screening are well known. One example is the events of 1994-1997 leading to Merck's marketing of the painkiller Vioxx, described in Gardiner Harris, *The Cure: With Big Drugs Dying, Merck Didn't Merge—It Found New Ones*, The Wall Street Journal, January 10, 2001, at A1 (provided as Appendix U). Merck's search for a novel pharmacologically suitable painkiller made use of *in vitro* screens to find drugs that inhibited the activity of Cox-2 but not Cox-1. Such drugs would inhibit prostaglandin production in most of the body but not the gut, thereby ameliorating pain while avoiding undesirable side effects. Candidate drugs from a collection of hundreds of synthesized drugs were first subjected to *in vitro* screening; a much smaller number of successful *in vitro* candidates advanced to *in vivo* screening in mice, and two successful nontoxic drugs from the mouse *in vivo* screens were advanced to even more expensive human clinical trials. Only one of these two drugs showed efficacy in clinical trials, ultimately received FDA approval, and is now being marketed as Vioxx. This example illustrates how a "real world" benefit can be obtained from distinguishing gene family members.

2. *The 2871 sequence has a high degree of identity to other sequences which have utility; therefore, the 2871 sequence has utility.*

The USPTO utility examination guidelines state, "[w]hen a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein." 66 Fed. Reg. 1096. In

the present application, Applicants have demonstrated that the 2871 receptor is a member of the rhodopsin family of G-protein coupled receptors. Members of this family of receptors are known by those of skill in the art to share a specific, substantial, and credible utility. In fact, it has come to our attention that a U.S. patent has issued from an international application disclosed by Applicant in the Supplemental IDS returned by the Examiner with paper 8 (the Office Action mailed 8/25/00). In U.S. Patent No. 6,063,596, (the '596 patent) with inventors Lal *et al.* and assigned to Incyte Pharmaceuticals, issued 16 May 2000, one of the disclosed sequences has 98% identity to Applicant's 2871 sequence. The claimed invention of the '596 patent is described as providing human G-protein coupled receptors associated with immune response. Applicants' present claims are directed to methods of using the 2871 sequence of the present invention. Because there is an issued U.S. patent with claims to sequences with a high degree of identity to Applicant's 2871 sequences, the Patent Office must have found these sequences to have utility. Accordingly, a rejection of Applicants' present claims for lack of utility is inappropriate and should be withdrawn.

3. *The present invention is useful in its currently available form.*

The Examiner has stated that the specification does not provide "any evidence or guidance suggesting the claimed protein's activity" (Examiner's Answer at page 3) and that therefore doubt is cast on "whether the nucleotide sequence or its encoded protein can be used in **any** of applicants asserted utilities." (emphasis added; Examiner's Answer at page 4). Applicants disagree. As discussed in the specification and known in the art, GPCRs (G-protein coupled receptors) are responsible for G-protein mediated signal transduction. "GPCRs, along with G proteins and...intracellular enzymes and channels modulated by G-proteins, are the components of a modular signaling system that connects the state of intracellular second messengers to extracellular inputs." (specification page 2; see also pp. 6, 7, 20).

While the Examiner's assertion of lack of utility may reflect the thinking of the pre-genomics era, it does not accurately describe the current state of the art in drug discovery. Those of skill in the art appreciate that rapid advances in technology have led to dramatic changes in the

way research is conducted in many biomedical-related areas. “Molecular biology has had a dramatic influence” on active drug discovery and research projects in the pharmaceutical industry, particularly those involving GPCRs. See Stadel *et al.* (1997) *Trends Pharmacol. Sci.* 18:430-436; provided as Appendix P). The advances in molecular biology have led to what those in the art consider a “paradigm shift” in the way research and drug discovery is conducted. *Id.* In this new paradigm, the starting point in the process is the identification of new members of gene families such as the GPCR superfamily by “computational or bioinformatic methodologies.” Stadel at 430. “Once new members of the GPCR superfamily are identified, the recombinantly expressed receptors are used in functional assays to search for the associated novel ligands. The receptor-ligand pair are then used for compound bank screening to identify a lead compound that, together with the activating ligand, is used for biological and pathophysiological studies to determine the function and potential therapeutic value of a receptor antagonist (or agonist) in ameliorating a disease process.” Stadel at 434; see also Fraser (1995), *J. Nucl. Med.* 36 (6 Suppl): 17S-21S (Appendix R). Often, these screens are implemented in high-throughput format. *See id.* Thus, in the molecular biology field of the present invention, the discovery of a novel sequence is the key step, or “first link” of *Cross*. *See, Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir. 1985) (holding that “[w]e perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question.”)

Similarly, in drug development, the key step or “first link” is the discovery of a novel sequence such as that of the present invention; subsequent screening steps are routinely performed. As those in the art note, “the potential reward of using this [“reverse molecular pharmacological strategy”] approach is that resultant drugs naturally will be pioneer or innovative discoveries, and a significant proportion of these unique drugs may be useful to treat diseases for which existing therapies are lacking or insufficient.” Stadel at 434.

As those in the art are aware, much is known about GPCRs but many details of GPCR activity remain to be resolved, including comprehensive information about the mechanisms and domains of previously discovered GPCRs. Despite this lack of encyclopedic knowledge about GPCRs, members of this gene family have been shown to bind a variety of ligands and have been

successfully used for drug discovery. See, for example, Stadel *et al.*, (1997) *Trends Pharmacol. Sci.* 18:430. "Because of the proven link of GPCRs to a wide variety of diseases and the historical success of drugs that target GPCRs, we believe that these orphan receptors are among the best targets of the genomic era to advance into the drug discovery process." Stadel at 436. "The fact that GPCRs mediate a broad spectrum of cellular events make these proteins an ideal target for drug interaction and therapeutics." Lee and Kerlavage (1993) *Molecular Biology of G-Protein-Coupled Receptors*, 6 DN&P 488 (Appendix T).

4. *The rejection of the claims under 35 U.S.C. §101 and §112, first paragraph, is inconsistent with USPTO guidelines and supporting case law.*

The Utility Examination Guidelines state, "Applicant[s] need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement." 66 Fed. Reg. 1098. This one-utility requirement is consistent with *Cross*, which held that "[w]hen a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown" *Cross*, 753 F.2d at 1046 fn9, citing *Raytheon Co. v. Roper Corp.* 724 F.2d 951, 958 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984). Thus, the Examiner's utility rejection depends on the invalidity of each of Applicants' asserted uses. However, as the Examiner noted (at page 3 of the Office Action mailed February 12, 2001 (paper 11)), "applicants do indeed provide multiple well-established and specific utilities for a GPCR." Inexplicably, the Examiner now states (at page 5 of the Examiner's Answer mailed August 28, 2001 (paper 18)) that "since there was no specific and substantial asserted utility or a well-established utility for the claimed nucleic acids and encoded proteins, credibility of the utility was not assessed."

The PTO guidelines state, "[a] rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record." 66 Fed. Reg. 1098. "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure...." 66 Fed. Reg. 1098. As the Examiner noted (at page 3 of the Office Action mailed Feb. 12, 2001 (paper 11)), Applicants "do indeed provide multiple well-established and

specific utilities for a GPCR,” and one of ordinary skill in the art would agree with the Examiner that the present invention satisfies the utility standard.

The PTO utility examination guidelines also state,

[w]here the asserted utility is not specific or substantial, a *prima facie* showing [of no specific and substantial credible utility] must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicants would be specific and substantial. The *prima facie* showing must contain the following elements: (1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed is not both specific and substantial nor well-established; (2) Support for factual findings relied upon in reaching this conclusion; and (3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

(66 Fed. Reg. 1098). Further, “[o]ffice personnel are reminded that they must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement” (66 Fed. Reg. 1098-99).

This provision is consistent with the case law. See, *In re Gazave*, 379 F.2d 973 (C.C.P.A. 1967) (finding that the utility standard was met where “appellant’s assertions of usefulness in his specification appear to be believable on their face and straightforward, at least in the absence of reason or authority in variance”); *Ex parte Dash*, 27 U.S.P.Q.2d 1481, 1484 (Bd. Pat. App. & Int’f 1993) (holding that “[a] disclosure of a utility satisfies the utility requirement of section 101 unless there are reasons for the artisan to question the truth of such disclosure.”) Similarly, in *In re Jolles*, claims to pharmaceutical compounds and methods of use were rejected under §101 and §112. The court held, “it is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct” (628 F.2d 1322, 1327 (C.C.P.A. 1980)). See also, *In re Brana*, 51 F.3d 1560, 1563 (Fed. Cir. 1995) (stating that “[o]nly after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicants to provide rebuttal evidence sufficient to convince such a person of the invention’s asserted utility,” and holding that the PTO did not meet this burden.)

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In the present case, the utility rejection has not been supported in the required manner. As discussed above, the Examiner's objections are not properly grounded in the authority cited and are in fact inconsistent with practices in the art. Accordingly, the Examiner has not made a *prima facie* showing of no utility and the rejection should be withdrawn.

CONCLUSION

In view of the arguments presented above, Applicants contend that each of claims 73, 74, 81, and 88-96 is patentable. Therefore, reversal of the rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, is respectfully solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

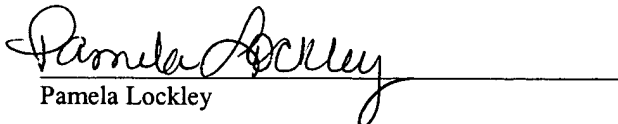


Leigh W. Thorne
Registration No. 47,992

CUSTOMER NO. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on October 29, 2001.


Pamela Lockley